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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,788	10/08/2003	Habib Zaghouani	07316.0002.CPUS01	6701

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,788	ZAGHOUANI ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/11/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13 and 15-30* is/are pending in the application.

4a) Of the above claim(s) *8-12,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,13,15-19 and 22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 8/08/08 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks filed 8/08/08, and IDS filed 8/11/08, have been entered.

2. Claims 8-12, 20, and 21 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, 7, 13, 15-19, 22-26, and newly added Claims 27-30 are under examination.

NOTE: Claim 25 has not been withdrawn.

3. Applicant's amended Abstract has been entered.

4. In view of Applicant's amendments the previous rejection under the first paragraph of 35 U.S.C. 112 for inadequate written description has been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 7, 13, 15-19, 22-26, and newly added Claims 27-30 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could effectively function as a method for preventing or delaying the onset of type I diabetes (IDDM).

As set forth previously, While the mechanism of action for the method of the instant claims is not disclosed, it appears to require inducing tolerance to GAD and altered GAD "derived" peptides. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models (EAE and collagen induced arthritis, respectively).

As set forth above, the references demonstrate that even unsubstituted peptides (peptides that are not APLs) that work in *in vivo* small animal disease models cannot be expected to work in humans. Regarding the even more unpredictable APLs, Anderton (2001), teaches that:

> "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders" (page 370).

Indeed, the reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*",

emphasis added.

A review of the instant specification shows just a single long example wherein a T cell response to a single insulin B chain peptide (amino acids 9-23) is inhibited in the experimental NOD mouse model of IDDM. First note that the instant claims are drawn to the use of GAD, not insulin, for the suspending, preventing or delaying the onset of IDDM. Thus, the specification offers *no* data in support of the claimed method. Interestingly, the specification discloses, that even regarding the use of an insulin peptide for the suspending, preventing or delaying the onset of IDDM, *the method of the instant claims cannot function as claimed*, emphasis added. For example, at page 28 of the specification, it is disclosed that, "Soluble Ig-INSβ displayed dose dependent delay of diabetes when given at either stage [pre or post IAA conversion]. However, aggregated Ig-INSβ, which induced IL-10 and TGFβ-producing T cells, thus involving sustained endogenous IL-10, was protective against diabetes when given before development of insulitis *but had no effect in predisposed mice positive for IAA*", emphasis added. Further, Examples 7 and 9 teach that neither soluble nor aggregated Ig-INSβ can actually prevent IDDM, but rather can only delay onset under specific conditions.

Additionally, Applicant's subsequent work demonstrates that the method of the instant claims would not be expected to function as claimed. See for example

Legge et al. (1998). Therein the authors teach that APLs function as, "T cell antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP-1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient. Given that *no* experiments have been performed employing GAD peptides and derivatives thereof, it is just as likely that the method of the instant claims would actually exacerbate disease as treat or prevent it.

A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses *no* data regarding the treatment or prevention of IDDM employing GAD peptides, and the unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 8/08/08, have been fully considered but are not found persuasive. Applicant argues that the utility rejection under 35 U.S.C., first paragraph should be withdrawn.

Applicant is advised that there is no utility rejection outstanding (35 U.S.C. 101). The instant rejection is for lack of enablement under the first paragraph of 35 U.S.C. 112.

At page 12 of the Remarks Applicant argues that data derived employing a NOD mouse model should be accepted, again citing the Inventor's 12/19/07 1.132 declaration.

The Inventor's declaration was addressed previously. Regarding the Inventor's 1.132 declaration, it appears that the Inventor has recently established some efficacy in the NOD mouse model employing an unidentified "soluble Ig-GAD2". The Inventor's results are noted, however, as set forth above, said results are not enabling for the use of the claimed method for the preventing or delaying the onset of IDDM in humans. Also, the work was apparently done after the effective filing date and

therefore cannot be relied upon to show enablement at the time of filing as is required.

Applicant argues that Couzin (2003), "does not evidence failure of the NOD model to predict success in humans" and, "No indication is found in Couzin that the researchers were in fact attempting to induce "tolerance to insulin.""

Regarding the induction of tolerance in mouse models, such is well-known to immunologists. That tolerance induced in mouse models has not translated to efficacy in humans is also well-known to the ordinarily skilled immunologist. Again, see the Abstract in Harrison (2008, of record). Regarding the DPT-1 trial referenced in Couzin, again it is well-known to the ordinarily skilled immunologist that the trial was indeed a failed attempt to induce tolerance in humans. For Applicant's edification a review of the results, including a description of the attempt to induce immune tolerance, is enclosed (see Skylar et al. (2005)).

Applicant cites Harrison (2008, of record) as "proof of concept".

A 2008 "proof of concept" cannot be considered enabling for the 2002 invention of the instant claims. Indeed, a "proof of concept" is evidence that an invention does not yet exist as a "concept" is not an "invention". Additionally, it is an Applicant's obligation to supply an enabling disclosure without reliance on what others *may* publish after he has filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in a position to file.

Applicant argues the separateness of the rejections for lack of enablement and obviousness, arguing that Applicant's have enabled the claimed invention. Applicant argues that the invention was unpredictable prior to the Applicant's invention. Interestingly, in the remarks regarding the obviousness rejection, Applicant argues a lack of expectation of success.

Applicant's arguments are noted but the claimed invention is not now enabled nor was it enabled at the time of filing. A review of the instant specification reveals *no* data employing the construct used in the claimed method. It is unclear then how Applicant can argue that the invention is both enabled for it's full scope, but at the same time unexpected. The

Examiner's more tenable position is that, while the invention might delay onset of diabetes in some experimental mice (and can thus be found to be obvious), it is not enabled for the preventing of disease in any species nor the preventing or delay of disease in humans.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 4, 5, 7, 13, 15-19, 22-24, and newly added Claims 28-30 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/30706 in view of Kaufman et al. (1992).

As set forth previously, WO 98/30706 teaches the treatment of autoimmune disorders, including IDDM, (see particularly pages 10 and 19) employing an engineered fusion protein, e.g., a humanized IgG_{2b} chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop (see particularly Figure 1, page 13, and Example II).

The method differs from the claimed invention only in that it does not teach the use of GAD65 as the autoantigen employed for the treatment of IDDM.

Kaufman et al. teach that GAD65 (which would comprise amino acid residues 206-220 and 524-543), along with insulin, is a well-known IDDM autoantigen (see particularly page 283, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of WO 98/30706 for the treatment of IDDM employing the autoantigen of Kaufman et al. One of ordinary skill in the art at the time the invention was made would have been motivated to select GAD65 as the autoantigen for use in the claimed method given the teachings of Kaufman et al. that GAD65 was one of the few known IDDM autoantigens at the time of the invention. Regarding the timing of administration of the Ig-fusion protein set forth in claims such as 3, 16, 17, etc., said timing would comprise only routine optimization which would fall well within the purview of one of skill in the art at the time of the invention.

Applicant’s arguments, filed 8/08/08, have been fully considered but are not found persuasive. Applicant argues a lack of asserted obviousness.

A review of the primary reference reveals that it is by the Inventor wherein he teaches that an identical immunoglobulin construct, save for the choice of inserted antigen, can be employed to treat diabetes. Thus, inserting one of the most well-known and well-characterized diabetes antigens into Applicant's own known immunoglobulin construct, and then using said construct to delay diabetes, would have been obvious.

Applicant argues no reasonable expectation of success. As set forth above, there is a reasonable expectation that the construct of the claims could be used to delay diabetes onset in experimental animals. Also note that the reference is Applicant's own work and Applicant says that the immunoglobulin construct can be used to treat diabetes. To now argue lack of expectation of success when faced with an obviousness rejection is not persuasive. Note that Claim 26 reciting a fragment consisting of specific residues of GAD65 is not included in the rejection because there is no teaching of employing only a specific 14 amino acid fragment. All other claims, however, encompass the use of full length GAD65 which is obvious.

Applicant argues that not all claim elements are taught by the references, specifically administration of the immunoglobulin construct after insulin autoantibody seroconversion.

Applicant is advised that the claimed method would be obvious for delaying diabetes at any stage in which it might still be delayed.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be

commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-5, 7, 13, 15-19, 22-25, and 27-30 stand/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/290,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '070 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-5, 7, 13, 15-19, 22-25, and 27-30 stand/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/425,084. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '084 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant defers a response regarding the remaining rejections until the finding of allowable claims.

12. The following are new grounds for rejection necessitated by Applicant's amendment.

13. Claims 1-5, 7, 13, 15-19, and 22-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art

that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter written description rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method comprising the administration of an immunoglobulin construct comprising a protein represented by SEQ ID NO:4 (Claims 1 and 13).

B) A method comprising the administration of an immunoglobulin construct comprising a peptide consisting of amino acid residues 206-220 of GAD65 (Claim 26).

Applicant cites pages 13, 21, 45, and 26 in support of the claimed method.

A review of the specification reveals that the peptide of SEQ ID NO:4 is found at page 46 of the specification. The specification, however, does not teach the peptides as part of an immunoglobulin construct. Further, the specification does not teach a peptide consisting of amino acid residues 206-220 of *any* GAD65, e.g., mouse GAD65, rat GAD65, horse GAD65, etc.

14. No claim is allowed.

15. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara, Ph.D. can be reached on (571) 272-0878.

17. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197

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